I. AMENDMENTS

A. In the Specification:

Please amend the first paragraph of page 1, to recite as follows:

"This ~~application~~ is a continuation application of U.S. Serial No. 09/856,127, now U.S. Patent No. 6,683,061, issued January 27, 2004, which ~~was filed under~~ is the National Stage of International Application No. PCT/US00/20008, filed July 21, 2000, which in turn claims [~~priority~~] the benefit under 35 U.S.C. § 119(e) to the following U.S. provisional applications, U.S. Serial Nos.: 60/145,356; 60/145,437; and 60/191,315, filed July 22, 1999; July 23, 1999 and March 21, 2000, respectively, the contents of which are hereby incorporated by reference into the present disclosure."

Please amend the specification at the following locations to recite as set forth below:

Page 51, line 18:

5-(4-Carbethoxy-1,3-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine

Page 52, lines 15 and 16:

(c) 5-(3-Oxoprop-1-enyl)-2'~~dexoyuridine~~ deoxyuridine -3',5'-bis(tetrahydro-2*H*-pyran-2-yl)ether (III)

Page 52, lines 26-27:

(d) 5-(4-Carbethoxy-1,3-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine -3',5'-bis(tetrahydro-2*H*-pyran-2-yl)ether (IV)

Page 53, lines 4 to 12:

(e) 5-(4-Carbethoxy-1,3-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine (V)

5-(4-Carbethoxy-1,3-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine -3',5'-bis(tetrahydro-2*H*-pyran-2-yl)ether (IV) (0.637 g, 1.22 mmol) was dissolved in MeOH (1.5 mL) and PPTS (0.049 g, 0.16 mmol) was added. The solution was stirred at 50°C for 7.5 h and left at room temperature overnight. A white precipitate was formed. The reaction mixture was cooled to 0°C and filtered to give pure (V) as a white solid (0.188 g). The filtrate was concentrated and chromatographed on silica gel using 50-100% EtOAc/hexane as eluent to give a further 0.180 g product. The total yield of the product was 0.368 g (86%).

Page 53, line 19:

5-(4-Carbomethoxy-1,3-butadienyl)-2'- ~~dexoyuridine~~ deoxyuridine (Va)

Page 54, lines 8 to 15:

5-(4-Carboxy-1,3-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine (VI)

5-(4-Carbethoxy-1,3-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine (V, from Example 1) (0.449 g, 1.28 mmol) was dissolved in 2N NaOH (3 mL) and stirred at 25°C. After 20 min, a precipitate was formed and TLC showed that the starting material was completely consumed. The mixture was cooled to 0°C and acidified to pH 1 with 2N HCl. The resulting off-white solid was filtered off, washed with water and dried *in vacuo* to give 0.225 g (54%) product.

Page 54, line 25 to page 55, line 20:

The title compound can also be prepared from 5-(4-carbomethoxy-1,3-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine (**Va**) (prepared according to the method in Example 2) in comparable yield as mentioned above.

Example 12

5-(4-Bromo-1*E*,3*E*-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine (VIIa) and

5-(4-Bromo-1*E*,3*Z*-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine (VIIb)

To a solution of 5-(4-carboxy-1,3-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine (VI) (0.200 g, 0.62 mmol) in DMF (1 mL) was added $KHCO_3$ (0.185 g, 1.84 mmol) and the

mixture was stirred for 20 min at 25°C. A solution of *N*-bromosuccinimide (0.117 g, 0.65 mmol) in DMF (0.3 mL) was added dropwise. Smooth gas evolution (CO_2) occurred throughout the addition. The resulting brown suspension was stirred for 2 h at 25°C at which time TLC showed that (**VI**) was completely consumed. Water (10 mL) was added to the suspension and the resulting solution was extracted with EtOAc (2 × 15 mL). The extract was dried over $MgSO_4$ and the solvent was evaporated *in vacuo* to give a yellow solid (178 mg, 80% yield) consisting of a mixture of two isomers as shown by ^{1}H NMR. The crude product was separated by semi-preparative HPLC (reversed phase C18 column) using 20% acetonitrile in water as the mobile phase to give the following isomers:

5-(4-Bromo-1*E*,3*Z*-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine: retention time 10.5 minutes; ^{1}H NMR: (DMSO-d_6): 2.11-2.18 (2H, m), 3.50-3.70 (2H, m), 3.80 (1H, distorted q, J = 3.5 Hz), 4.25 (1H, br s), 5.08 (1H, br s), 5.25 (1H, br s), 6.15 (1H, t, J = 6.5 Hz), 6.40 (1H, d, J = 7 Hz), 6.53 (1H, d, J = 15.6 Hz), 6.83 (1H, dd, J = 7, 10 Hz), 7.39 (1H, dd, J = 10, 15.6 Hz).

5-(4-Bromo-1*E*,3*E*-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine: retention time 15.1 minutes; ^{1}H NMR (DMSO-d_6): 2.12-2.16 (2H, m), 3.50-3.70 (2H, m), 3.80 (1H, q, J = 3.2 Hz), 4.26 (1H, m), 5.13 (1H, br s), 5.25 (1H, br s), 6.14 (1H, t, J = 6.5 Hz), 6.36 (1H, d, J = 15.6 Hz), 6.67 (1H, d, J = 13.1 Hz), 6.84 (1H, dd, J = 11, 13.1 Hz), 7.04 (1H, dd, J = 11, 15.6 Hz).

Page 55, lines 23 to 27:

Using the procedures mentioned in Example 3, Method II, the following compounds can be obtained in a similar fashion: 5-(4-chloro-1,3-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine (using *N*-chlorosuccinimide in place of *N*-bromosuccinimide in Step B); 5-(4-iodo-1,3-butadienyl)-2'-dexoyuridine (using iodine in sodium idodide in place of *N*-bromosuccinimide).

Page 53, line 20:

5. 5-(4-carbomethoxy-1,3-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine,

Page 70, lines 10 to 18:

The compound NB1024 as tested above consists of a mixture of two isomers, 5-(4-Bromo-1*E*,3*E*-butadienyl)-2'-~~dexoyuridine~~ deoxyuridine (VIIa), (Isomer 1), and 5-(4-Bromo-1*E*,3*Z*-butadienyl) -2'-dexoyuridine (VIIb), (Isomer 2). These two compounds were separated by semi-preparative HPLC (reversed phase C18 column) using 20% acetonitrile in water as the mobile phase as described above (Example 4). The ability of each isolated compound to block cell proliferation was then determined by the crystal violet procedure. Results are shown in Table 7. The two isomers display markedly different activities with the Z isomer, Isomer 1, showing significantly greater growth inhibiting activity in comparison with the E isomer, Isomer 2.

Please add the following sequence listing to the disclosure of the application.

SEQUENCE LISTING

<110> Shepard, Michael H.

Chan, Ming Fan

Groziak, Michael P.

<120> ENZYME CATALYZED THERAPEUTIC ACTIVATION

<130> NB 2008.01

<140> 10/681,418

<141> 2003-10-07

<150> PCT/US00/20008

<151> 2000-07-21

<150> 60/145,356

<151> 1999-07-22

<150> 60/145,437

<151> 1999-07-23

<150> 60/191,315

<151> 2000-03-21

<150> 09/856,127

<151> 2001-10-10

<160> 4

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 19

<212> DNA

<213> Homo sapiens

<400> 1

gggcagatcc aacacatcc 19

<210> 2

<211> 20

<212> DNA

<213> Homo sapiens

<400> 2

ggtcaactcc ctgtcctgaa 20

<210> 3

<211> 19

<212> DNA

<213> Homo sapiens

<400> 3

gccaacacag tgctgtctg 19

<210> 4

<211> 19

<212> DNA

<213> Homo sapiens

<400> 4

ctcctgcttg ctgatccac 19